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Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue N.W.
Washington, D.C. 20460

March 9, 2007

Dear Administrator:

On behalf of the Eastman Chemical Company, I wish to thank the Environmental Protection Agency (EPA) for their comments on the test plan and robust summaries for Ketone Bottoms (KB4/KB3), CAS No. 68990-20-5. Since 2000, Eastman Chemical Company has supported the collection and review of available test data, development of test plans and robust summaries, and conducted additional testing.

Based on our initial recommendations and the peer-reviewed comments of the EPA, Eastman Chemical is pleased to submit the following revised test plan and robust summaries for this substance. The revised test plan and robust summaries contain additional data on existing studies and the results of additional new toxicity studies that are related to the questions and comments made by the EPA in its letter dated 06/30/2005. This letter contains responses to the specific comments made by the EPA. These responses taken together with the inclusion of new study data and other information constitute the key changes to the original test plan and robust summaries.

Based on these additional data, the Eastman Chemical Company concludes that the current test plan and robust summaries is now complete. The experimental and model data for physiochemical properties, environmental fate, ecotoxicity, and human health endpoints are consistent and provide a comprehensive basis upon which to evaluate the hazard potential of Ketone Bottoms (KB4/KKB3).

We consider that the test plan and robust summaries are final and have no plans to provide additional data. The EPA comprehensive comments provided the necessary guidance to complete the test plan for this category. The collaboration between the Eastman Chemical Company and the Environmental Protection Agency in the Chemical "Right to Know" Program has produced a hazard database that will be useful to the public for decades to come. Thank you for the opportunity to participate in such a program.

If you have any questions or comments concerning the contents of this letter, please feel free to contact me at any time (202-331-2325) or tadams@therobertsgroup.net.

Best regards,

Timothy B. Adams, Ph.D.

Technical Contact Person for Eastman Chemical Company

201-16569A

**EPA Comments on Chemical RTK HPV Challenge Submission:**

**Ketone Bottoms (KB4/KB3)**



**Summary of EPA Comments**

The sponsor, Eastman Chemical Company, submitted a test plan and robust summaries to EPA for Ketone Bottoms (KB3/KB4) (CAS No. 68990–20–5) dated December 30, 2003. EPA posted the submission on the ChemRTK HPV Challenge Website on March 2, 2004.

EPA has reviewed this submission and has reached the following conclusions

1. 1. Physicochemical Data. The submitted data for these endpoints are adequate for the purposes of the HPV Challenge Program.
2. 2. Environmental Fate. The submitter needs to provide measured ready biodegradation data for additional components to adequately address this endpoint.
3. **Additional biodegradation data has been added for higher molecular weight ketones (C-11). Experimental data is available to relate biodegradability to the full range of constituents of the KB4/KB3 mixture.**

4. 3. Health Effects. EPA considers it inappropriate to use individual component data to characterize the toxicity of the two ketone bottom mixtures because of the uncertainty resulting from the absence of toxicity data on the significant undefined portion of each mixture. The submitter needs to conduct testing on KB4 and KB3 mixtures to adequately address these endpoints.

**While we agree that the toxicity testing of substances of known composition provides the optimum hazard information, testing of mixtures has severe limitations on the relevance of the hazard data generated. Based on the variation in the composition of the both KB4 and KB3 distillates, toxicity data would be applicable only to the given composition at a given time point in the production process. A more practical approach is to evaluate the constituents of the mixture, that exhibit the highest potential for toxicity. Studies of chemicals of greatest toxic potential provides a practical gauge of toxic potential for the mixture.**

**Base on the original data provided the only significant hazard concern is related to the neurotoxic potential of aliphatic linear, branched-chain, and alicyclic ketones in the KB4/KB3 mixture. This is a well-studied phenomenon that has been the subject of many structure activity-neurotoxicity studies. Therefore, it is difficult to evaluate the EPA responses, since concern for neurotoxicity has be expressed for ketones that do not possess the structural feature to potentially produce metabolites associated with peripheral neuropathy as observed for marker substances such as 2-hexanone. Clearly, the additional studies included for 2,6,8-trimethyl-4-nonanone and 2-pentadecanone show no evidence of toxicity at dose levels up to and including 1000 and 50 mg/kg/day, respectively. If toxicity data not relevant to human health is accounted for (alpha-2u-microglobulin effect in rats), no constituent of the KB4/KB3 mixture shows any adverse effects below 100 mg/kg bw/day.**

**We agree with EPA that insufficient hazard data existed for higher molecular weight ketones (C-11 to C-12). Therefore, we have included biodegradation, ecotoxicity, repeat dose, reproductive, and developmental toxicity data for a C-11 ketone, 2,6,8-triethyl-4-nonanone. For those endpoints related to human health, there is no evidence of neurotoxicity for this substance in any study.**

5. 4. Ecological Effects. EPA agrees that fish acute toxicity data are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide additional invertebrate and algae test data because the submitted data do not adequately represent the range of chemicals in the mixtures. EPA recommends that the submitter test a chemical within the C10-C12 range. Chronic daphnia toxicity data are needed for the most hydrophobic known component in the mixtures. The submitter needs to include some missing data elements in the robust summaries.

**In the interest of completeness, ecotoxicity for fish, invertebrates, and aquatic plants has been provided for the C-11 ketone, 2,6,8-trimethyl-4-nonanone. These data provide ecotoxicity experimental data for constituents C-7 through C-12.**

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

## EPA Comments on the Ketone Bottoms (KB4/KB3) Challenge Submission

### Test Plan

Test Substance Identification

Ketone bottoms are presented as two mixtures (KB4 and KB3) under one CAS number. KB4 contains approximately 50% linear- and branched-chain $C_9$-$C_{12}$ aliphatic ketones. Other known constituents include mixed dimethylcyclohexanones (10.8%) and 6-methyl-2-heptanone (2.5%). The submitter anticipates the remaining ~37% of KB4 to be a complex mixture of ketones of similar molecular weight and structure. KB3 is a mixture of linear and branched-chain aliphatic ketones and alkyl-substituted cyclohexanones: >35% undecanone isomers, 11% cyclohexanone, 5% pentadecanone derivatives and other $C_{11}$ –$C_{15}$ ketones.

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The submitted data for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data for photodegradation, stability in water, and fugacity are adequate for the purposes of the HPV Challenge Program.

*Biodegradation*. The experimental data provided by the submitter do not adequately describe the biodegradation behavior of the range of known components that make up the KB3 and KB4 substances. Experimental data on two analogues and estimated data (BIOWIN) on some components are not sufficient to address this endpoint for the purposes of the HPV Challenge Program because the biodegradation potential of the various ketone components will depend on chain length, degree of branching, carbonyl position and the presence of cyclic structures. The data provided by the submitter do not address these structural differences. The submitter needs to provide measured ready biodegradation data on enough components to address this variety of structures.

**Experimental biodegradation has been provided for C-7 to C-11 ketones. Based mainly on OECD 301D guideline studies, experimental and model data on C-11 ketones suggests that ketones greater than C-11 are not biodegradable.**

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitter needs to conduct testing using KB4 and KB3 mixtures to adequately address these endpoints.

The submitter provided no human health data for the mixtures KB4 and KB3 themselves. Although the submitter provided toxicity and metabolism data for selected components or their analogs, the test plan (1) did not adequately support the validity of using test data for individual components of a mixture for characterizing the toxicity of that mixture; (2) did not present a logical approach for integrating data for individual components of KB3/KB4 to qualitatively and quantitatively characterize the toxicity of these mixtures; and (3) did not present a means to address the uncertainty caused by the absence of toxicity data on the significant undefined portion of each ketone bottom mixture (~37% of KB4 and ~44% of KB3).

**1) Without guidance from EPA on specific inadequacy of the use of test data on constituents of the KB4/KB3 mixture, we have added additional data on higher molecular ketones to support our conclusions that hazard data for the most toxic constituents can be used to evaluate the toxic potential of the mixture. With the additional human health data for a C-11 and C-12 ketones, human health related toxicity data is now available for the range of ketones from C-7- through C-15 ketones. As indicated in the original submission, the principal component of hazard concern is 5-nonanone. On a molar basis, other constituents are of similar low toxic potential.**

**2) The data is intended to present an empirical basis for evaluating the hazard data, not a logical defense of the data. With the exception of ketones exhibiting peripheral neuropathy (e.g., 5-nonanone), there is no significant differences in toxicity between C-7 and C-15 ketones on a molar basis.**

**3) As for the undefined portion of the KB4/KB3 mixtures, the unknowns are ketones of linear, branched-chain and alicyclic structure. There is no evidence that the unknown fraction contains non-ketone materials. Also, the level of unknowns is similar to that for chemically defined substances such as camphene that contain as much as 30% unknown. These material have been adequately evaluated the OECD SIDS program.**

The test plan described some similarities in metabolism/excretion of the known ketone constituents of KB4 and KB3 and related chemicals to justify the use of analogs to represent individual component chemicals; however, it is not possible to predict whether such pathways pertain to the significant portion of each mixture that is not defined. For example, the test plan (page 11) mentioned that 5-nonanone can be metabolized to a neurotoxic gamma-diketone, and that 5-nonanone is the only ketone in the KB4 mixture containing structural features that permit a neurotoxic gamma-diketone to form. The test plan also indicates that 5-nonanone when given to animals in a pure form at a certain dose level (233 mg/kg bw), did not show signs of general or neurological toxicity. However, when present in a mixture at this level (approximately 11%) it showed signs of neurotoxicity and peripheral neuropathy, suggesting that 5-nonanone acts as a synergist. Given the fact that approximately 37% of the KB4 mixture is not characterized and the uncertainty as to the potential for forming a neurotoxic gamma-diketone, EPA believes that testing on the mixture is warranted.

**Response: In order to clarify the studies performed by O'Donohogue concerning neurotoxicity, we have revised the test plan to better reflect the results on 5-nonannone and on the mixture of 5-nonanone and 5-methyl-2-octanone. First there is experimental evidence that 5-nonanone shows slight neuropathic effects at 233 mg/kg bw after 90 days. As the author noted "dose levels of 1000 mg/kg of 5-nonanone have been shown to produce clear evidence of "giant axonal swelling" neurotoxicity and doses of 233 mg/kg bw show early indications of "giant axonal swelling". Doses below 200 mg/kg are not expected to produce any such neurotoxic effects. The results of studies on the mixture and on the pure substance are, therefore, mutually consistent. There is no strong evidence for a synergistic effect.**

Most of the data presented for human health effects were for KB4 components or their analogs; no data were provided for components of KB3. Therefore, it does not appear possible to predict the human health

effects of KB3 from existing submitted data.

**Response: While we agree that there is more hazard data for KB4 constituents, KB3 constituents are structurally so similar to KB4 constituents, that current toxicity studies are not sufficiently sophisticated to evaluate the difference in toxicologic potential between these ketone analogs.**

Ecological Effects (fish, invertebrates, and algae)

*Fish.* EPA agrees that the data are adequate for the purposes of the HPV Challenge Program.

*Invertebrates and Algae.* The submitter needs to provide additional measured invertebrate and algae acute toxicity data because the submitted data do not represent the range of chemicals in the mixtures. EPA recommends that the submitter consider testing a chemical(s) in the C10-C12 range. In addition, chronic daphnia toxicity data are needed for the most hydrophobic known substance in each mixture that is accessible for testing.

**Response: As recommended by EPA, acute studies for fish, aquatic invertebrates, and aquatic plants have been performed for a C-11 ketone. The studies were performed at the limit of solubility for the substance, 2,6,8-trimethyl-4-nonanone, in the three studies.**

**Specific Comments on the Robust Summaries**

Ecological Effects

*Fish and Invertebrates.* The submitter needs to include water solubility and log Kow input values in robust summaries for SAR data.

**Response: These data were included where available.**